25 June 2015
EMA/CHMP/512637/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aripiprazole Sandoz

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/004008/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the Ph.Eur.
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control test
IR	Infrared
KF	Karl Fischer Titration
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification / Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder

mg	milligram
MS	Mass Spectrometry
MS	Member State
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalopathy
UV	Ultraviolet
XRPD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 10 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Aripiprazole Sandoz, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

- treatment of schizophrenia in adults and in adolescents aged 15 years and older.

- treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

- treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC) for 5 mg, 10 mg, 15 mg, 30 mg; Hybrid application (Article 10(3) of Directive No 2001/83/EC) for 20 mg.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Abilify instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Abilify 5mg, 10 mg, 15mg, 30mg tablets
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd.
- Date of authorisation: 09/06/2004
- Marketing authorisation granted by:
  - Community

- Community Marketing authorisation number: EU/1/04/276/001-020

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: **Abilify 5mg tablets**
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd.
- Date of authorisation: 09/06/2004
- Marketing authorisation granted by:
  - Community
  - (Community) Marketing authorisation number(s): EU/1/04/276/001-005
- Bioavailability study number(s): 2013-06-TAB-1/3020/13
- Product name, strength, pharmaceutical form: **Abilify 10mg tablets**
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd.
- Date of authorisation: 09/06/2004
- Marketing authorisation granted by:
  - Community
  - (Community) Marketing authorisation number(s): EU/1/04/276/006-010
- Bioavailability study number(s): 2013-05-TAB-1/3021/13

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

Lek Pharmaceuticals d.d.
Verovskova ulica 57
SI-1526 Ljubljana
Slovenia

Lek S.A.
ul. Domaniewska 50C,
Warszawa, 02-672,
Poland

S.C. Sandoz S.R.L.
Str. Livezeni nr. 7A
Târgu Mureş
jud. Mureş
540472
Romania

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 10 June 2014.
- The procedure started on 23 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014.
- During the meeting on 6 November 2014, the PRAC adopted the PRAC Rapporteur's Risk Management Assessment Report.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 November 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 January 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 March 2015.
- During the meeting on 12 March 2015, the PRAC adopted the PRAC Rapporteur's Risk Management Assessment Report.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 May 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 2 June 2015.
- During the meeting on 11 June 2015, the PRAC adopted the PRAC Rapporteur's Risk Management Assessment Report.
- During the meeting on 25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Aripiprazole Sandoz.

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation for Aripiprazole Sandoz concerns a generic medicinal product of the centrally authorised product Abilify, which, at the time of this report, was available as tablets (5mg, 10mg, 15mg and 30 mg), orodispersible tablets (10mg, 15mg and 30 mg), oral solution (1 mg/ml) and solution for injection (7.5 mg/ml).

This centralised application initially concerned a generic application according to article 10(1) of Directive 2001/83/EC as amended for Aripiprazole Sandoz 5mg, 10mg, 15mg and 30mg tablets and a hybrid of the reference product (Abilify) according to article 10(3) of Directive 2001/83/EC as amended for Aripiprazole Sandoz 2mg and 20mg tablets. The applicant is Sandoz GmbH. The 2mg strength was withdrawn during the procedure.

Aripiprazole is a quinolinone derivative, 7-{4-[4-(2, 3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone, which exerts both agonistic and antagonistic activity at dopaminergic and serotonergic receptors, along with activities at other receptors. Abilify is approved for treatment of schizophrenia and manic episodes in Bipolar I Disorder as well as the prevention of manic episodes as follows:

> *ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.*
>
> *ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.*
>
> *ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.*

The efficacy of Aripiprazole in schizophrenia and Bipolar I Disorder is thought to be mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. For the treatment of schizophrenia, aripiprazole is given in an initial oral dose of 10 or 15 mg once daily. The recommended maintenance dose is 15 mg once daily. For the treatment of acute manic episodes in bipolar disorder, the recommended initial oral dose is 15 mg once daily as monotherapy, or combination therapy. For preventing recurrence of manic episodes, it is recommended to continue therapy at the same dose administered for treatment of acute episodes. The maximum daily dose should not exceed 30 mg.

Two bioequivalence studies have been performed using the originator as a reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 5 mg, 10 mg, 15 mg, 20 mg or 30 mg of aripiprazole as active substance.

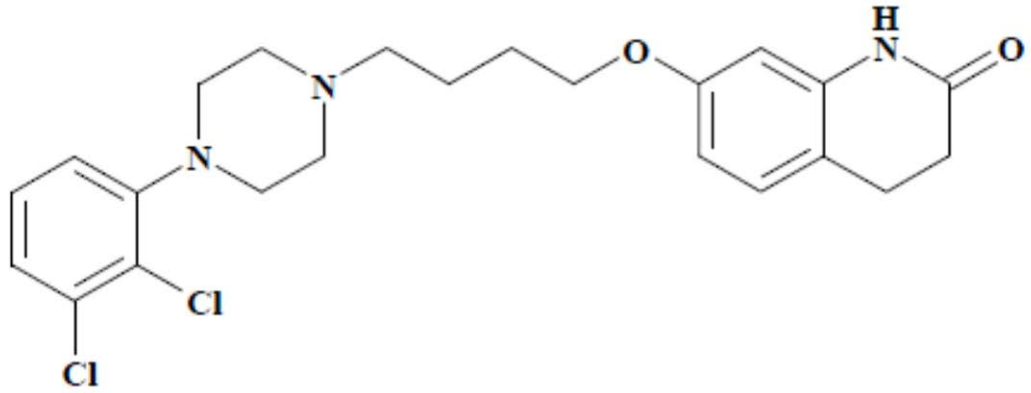
Other ingredients are: lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate in common for all tablets; indigo carmine aluminium lake (E132) for 5 mg tablets, red iron oxide (E172) for 10 mg tablets and 30 mg tablets, and yellow iron oxide (E172) for 15 mg tablets.

The product is available in aluminium/aluminium blisters in carton box for all tablets and high density polyethylene (HDPE) bottles containing a silica gel desiccant and a polyester coil for 5 mg, 10 mg, 15 mg and 30 mg tablets.

2.2.2. Active substance

General information

The chemical name of aripiprazole is 7-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one and has the following structure:



The structure has been confirmed using elemental analysis, mass spectrometry, IR, UV, ^{1}H-NMR and ^{13}C-NMR spectroscopy, X-ray powder diffraction and differential scanning calorimetry.

Aripiprazole is a white to off-white powder, freely soluble in N, N-dimethylacetamide and tetrahydrofuran, slightly soluble in ethanol and methanol, and practically insoluble in water. Solubility in water is slightly increasing at lower pH.

Aripiprazole has a non-chiral molecular structure. Polymorphism has been observed for aripiprazole. Ten crystalline solid state forms have been identified based on literature: five polymorphs, a monohydrate, and four solvates.

Manufacture, characterisation and process controls

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Aripiprazole is obtained from a single manufacturer.

Aripiprazole is synthesized in four main steps using commercially available well-defined starting materials with acceptable specifications. During the evaluation procedure, the active substance starting materials were redefined to ensure full control of the quality of the active substance in line with ICH Q11.

Several compounds originating either from starting materials or from the synthesis of aripiprazole have a structural alert for genotoxicity and satisfactory data is presented to demonstrate that the manufacturing process proposed is capable of removing or purging these compounds to acceptable limits in line with the current guidelines.

Potential and actual impurities were sufficiently discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in two high molecular high density polyethylene bags or two antistatic high molecular high density polyethylene bags which comply with the EC directive 2002/72/EC and EC 10/2011.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for: appearance (visual examination), identity and polymorphic form (IR, XRPD), loss on drying, residual solvents (GC), impurities (HPLC and GC), sulfated ash (Ph. Eur.), assay (HPLC), and particle size distribution (laser diffraction).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Batch analysis data on eight commercial scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for 60 months under long term conditions at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance (visual examination), identity (HPLC, IR, and XRPD), loss on drying/ water content (KF), impurities (HPLC), and assay (HPLC). The analytical methods used were the same as for release and were stability indicating. During stability testing, the method for water content (KF) was replaced with the loss on drying method, in order to align the tests with those published in Ph. Eur. monograph for aripiprazole.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently

stable. The stability results justify the proposed retest period of 60 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of pharmaceutical development was to develop a stable tablet formulation that is bioequivalent to the reference medicinal product Abilify tablets.

During pharmaceutical development the solubility of several crystal forms of the active substance was studied. The active substance manufacturer consistently produces the single polymorphic form chosen for further development. This has been demonstrated using XRPD method suitable for differentiating the polymorphic form obtained from other forms reported. In addition, it has been demonstrated that polymorphic form does not change during manufacture and shelf-life of the finished medicinal product.

The active substance particle size effect on dissolution of the tablets was discussed and it has been demonstrated that dissolution method can detect changes in particle size distribution of the active substance. In order to control this effect, adequate limits for particle size distribution were set in the active substance specifications.

The discriminatory power of the dissolution method has been demonstrated.

The selection of excipients was primarily based on the composition of the reference medicinal product and the results from compatibility studies of the active substance with individual excipients. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards or EU legislation. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulations of generic Aripiprazole Sandoz tablet strengths (5 mg, 10 mg, 15 mg and 30 mg) are qualitatively the same as the formulations of equivalent tablet strengths of reference medicinal product Abilify. The formulation of hybrid Aripiprazole Sandoz tablet strength (20 mg) is qualitatively identical to 20 mg Abilify tablets marketed in USA and Canada. In Europe the 20 mg strength is a non-generic strength, developed to ease dosing (dose titration) in patients.

The formulations used during clinical studies are the same as those intended for marketing.

Two bioequivalence studies were performed showing bioequivalence between the 5 mg and 10 mg tablets and the reference product.

A request for biowaiver of 15 mg, 20 mg and 30 mg tablet strengths was submitted. In order to comply with requirements for biowaiver specified in the Guideline on the Investigation of Bioequivalence, comprehensive dissolution data was provided during the evaluation procedure. Requirements for biowaiver of 15 mg, 20 mg and 30 mg tablets were fulfilled.

Different approaches were tried during finished product manufacturing process development. Fluidized bed granulation was chosen as the manufacturing method of the finished product.

The primary packaging is included in section 6.5 of the SmPC. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of either of eight or nine main steps, depending whether colourant is used: sifting, mixing, fluid bed granulation of pre-mixture, drying, sifting/ sizing, mixing with colourant (for 5 mg, 10 mg, 15 mg, and 30 mg tablets), mixing with sized granules, compression and packaging. The granulation has been identified as a critical step. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual examination), average mass (weighing), disintegration (Ph. Eur.), water content (KF), identification (HPLC, TLC), assay (HPLC), uniformity of dosage units (HPLC), related substances (HPLC), dissolution (HPLC), and microbiological contamination (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results were provided for three commercial scale batches per tablet strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial size batches of 5 mg, 10 mg, 20 mg, and 30 mg tablets stored in aluminium/aluminium blisters under long term conditions for 24 months at 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

In addition, stability data of three commercial size batches of 5 mg, 10 mg, and 30 mg tablets stored in high density polyethylene bottles under long term conditions for 24 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Finally, in-use stability data of two commercial size batches of 5 mg and 30 mg tablets stored in high density polyethylene bottles under long term conditions for 36 months at 25 ºC / 60% RH according to the ICH guidelines were provided.

The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested using the same analytical procedures as the ones used at release. The analytical procedures used are stability indicating.

In addition, one batch of each of the strengths was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

All results complied with the proposed specification at all time points tested. Therefore, based on available stability data, the shelf-life of 2 years (3 months after first opening of bottle) with no special storage conditions are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Aripiprazole Sandoz is considered unlikely to result in any significant increase in the combined sales volumes for all aripiprazole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

For a generic of a reference medicinal product no toxicological and pharmacological tests are required. The CHMP concluded that no additional non-clinical data were required.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for 4 different strengths of aripiprazole tablets (5mg, 10mg, 15mg and 30mg) and one new strength (20mg) being introduced as an hybrid of the Reference medicinal product on the basis that this may facilitate dosage titration.

To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fasting conditions. These studies were the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of aripiprazole based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version, is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

As per *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98/Rev. 01/Corr**)*, the following criteria must be met for a waiver of additional strengths:

According to the current GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**), a bioequivalence study investigating only one strength for each pharmaceutical form may be acceptable if all of the following 5 conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturing process;
- the drug pharmacokinetics is linear;
- the qualitative composition of the different strengths is the same;
- the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule);

- the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Based on the BE study using the 10mg strength, a bio waiver for the 15 mg, 20 mg and 30 mg strengths was requested. The 10mg strength was chosen for the safety of the healthy volunteers in the study. This was considered acceptable and concurs with the guideline which states that the selection of the lower strength is justified for drugs showing linear pharmacokinetics in cases higher strengths cannot be safely administered in healthy volunteers. Life threatening adverse events attributed to acute laryngeal dystonia have been indeed reported following administration of a single dose of 30mg aripiprazole to healthy volunteers in bioequivalence studies. The 5mg strength has also been tested for bioequivalence versus the respective strength of the reference formulation.

The proposed 2mg strength applied for via Article 10.3 was intended to facilitate the initiation of the treatment in adolescents aged 13 and older. The applicant withdrew this strength during the procedure.

In addition, Aripiprazole showed linear kinetics over a range of 5 mg to 30 mg after single dose oral administration; hence it was deemed justified to claim a waiver for the additional strengths. All the conditions of the biowaiver for the 15mg strength were also considered fulfilled.

2.4.2. Pharmacokinetics

To support the application, the applicant has submitted **two** bioequivalence studies.

Study 2013-05-TAB-01:3021/13

Methods

This was a randomised, open-label, two-period, two-sequence, two-treatment, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Aripiprazole 10 mg tablets (Hexal AG) and Abilify 10 mg tablets (MAH: Bristol Myers Squibb GmbH) in 48 healthy, adult, male human subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Aripiprazole 10 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods each volunteer received a single oral dose of Aripiprazole 10mg Tablet with 240ml of water in period I and either one tablet of the reference or test product in period II.

Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 8 hours following drug administration. Drinking water was not permitted one hour before dosing and until one hour post dose. Subjects were confined to BPSI clinical facility from at least 12 hours prior to each drug administration until after the 72-hour blood sample collection in each study period.

The two periods were separated by a wash-out phase of at least 45 days.

Blood samples were taken at the following time points: pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours after dosing. Blood sampling time adjustments are presented in the dossier.

All plasma samples were shipped by courier, frozen in dry ice, and were received frozen and in good condition.

Test and reference products

Product Characteristics	Test product	Reference Product
Name	Aripiprazole 10 mg tablet	Abilify® (Aripiprazole) 10 mg tablets
Strength	10 mg	10 mg
Dosage form	Tablet	Tablet
Manufacturer	[redacted]	Marketing authorization holder: Bristol-Myers Squibb GmbH & Co. KGaA, Germany
Batch number	[redacted]	3C82104
Batch size(Biobatch)	[redacted]	[redacted]
Measured content(s) (% of label claim)	[redacted]	
Commercial Batch Size	[redacted]	[redacted]
Expiry date (Retest date)	[redacted]	03/2014
Location of Certificate of Analysis	[redacted]	[redacted]
Member State where the reference product is purchased from:	[redacted]	Germany
This product was used in the following trials:	Study no. 2013-05-TAB-1 [redacted]	Study no. 2013-05-TAB-1 [redacted]

Population(s) studied

48 healthy adult male human subjects were enrolled as per the protocol. The study started with 48 subjects and 38 completed the study. The reasons for10 exclusions has been included in the dossier and are deemed not to have an effect on the outcome of the study.

Main inclusion criteria:

Healthy human adult literate male non smoker subjects between 18-45 years of age (inclusive), having a body mass index (BMI) between 18.5 and 30 kg/m2 (inclusive) who had no evidence of underlying disease or

clinically significant abnormal laboratory values at screening and who voluntarily consented to participate in the study in written form.

Analytical methods

Analysis of aripiprazole was performed using test method AL-M166-04.

This method involved the extraction of aripiprazole and the internal standard aripiprazole-d8 from human plasma. Samples were kept frozen at -20ºC prior to analysis for a period of 59 days.

4092 blood samples were to be collected for the 48 subjects. 2046 samples were collected. 3 samples were re-assayed and 172 samples were identified for incurred sample reanalysis. 100.00% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

The method has been validated (MVR-166/02) and partially revalidated 8 times. The following parameters were addressed; selectivity of Aripiprazole and the internal standard (IS), calibration curve (linearity), carryover test, recovery of both the analyte and the internal standard, precision, accuracy, dilution integrity accuracy and precision, stability of the stock solution (short and long term stability in the biological matrix, bench top, freeze-thaw, auto sampler storage, and post-preparative stability), haemolysis effect accuracy and precision, ruggedness and matrix effect. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

The effect of interfering drugs was also studied using the following commonly used medicines: caffeine, cetirizine, diclofenac ibuprofen, paracetamol, nicotine, and ondansetron. No effect on the determination of the analyte and the internal standard was observed.

The lower limit of quantification (LLOQ) of this method for the estimation of Aripiprazole concentrations in plasma was 0.404ng/ml (Precision 3.82%, Accuracy 98.02%). The linearity range of Aripiprazole was from 0.404g/ml to 255.413ng/ml. (8 point curve)

The bioanalytical report (3021/13) was submitted with 20% of the subject chromatograms presented as well as the method SOP. Certificates of analysis for the test and reference drug products as well as for the drug standards used for Aripiprazole and Aripiprazole –d8 have been provided and are deemed acceptable.

Pharmacokinetic Variables

Primary parameters: AUC_{0-72} and C_{max}

Secondary parameters: T_{max}, $t_{½}$, K_{el} and NKEL (Number of points used in the calculation of terminal elimination rate constant).

Bioequivalence criteria; The 90% confidence interval of the relative mean AUC0-72 and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The 90% confidence interval of the relative mean AUC0-72 and Cmax of the test and reference product should be at least 80% and not more than 125% for log-transformed data. ANOVA was performed on the log-transformed pharmacokinetic parameters - AUC0-72 and Cmax of aripiprazole using General Linear Model (PROC GLM procedure) of SAS. The 90% confidence interval for the difference between the least square means (LSM) was calculated for the log-transformed pharmacokinetic parameters - AUC0-72 and Cmax of aripiprazole. The number of observations, arithmetic mean, standard deviation, coefficient of variation (CV %), minimum, median, maximum and geometric mean were calculated for all the pharmacokinetic parameters.

Results

Pharmacokinetic parameters for Aripiprazole 10mg (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	SD(±)	arithmetic mean	SD(±0
$AUC_{(0-72h)}$	1870.79	428.231	2038.49	412.031
C_{max}	48.20	11.550	52.31	10.839
T_{max}*	4.15	1.428	4.11	1.507

<AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours>

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

C_{max} maximum plasma concentration

T_{max} time for maximum concentration (* median, range)

Statistical analysis for Aripiprazole 10mg (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$ (ng/ml)	90.97%	86.81-95.33%	12.11

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
C_{max} (ng/ml)	91.36%	85.12-98.06%	17.30
* estimated from the Residual Mean Squares			

Safety data

There were 26 adverse events reported in the study which were related to the investigational products. AEs that were reported during the study included Body ache, Vomiting, Nausea, Giddiness, Vasovagal Syncope, Dyspepsia, Elevated Creatine Kinase (CK) levels, Giddiness, Fever, Headache, Fatigue and Backache. Among the 26 related adverse events 14 adverse events were assessed to be related to the test product and 12 adverse events were assessed to be related to the reference product. All adverse events were mild to moderate in intensity, followed up until resolution and resolved completely without sequelae. There were no serious adverse events in the study. Based on the review of the clinical and laboratory safety data, both the study products were found to be safe and well tolerated.

Pharmacokinetic Conclusion

Based on the presented bioequivalence study Aripiprazole 10mg tablets of Hexal AG is considered bioequivalent with Abilify 10mg tablets of Bristol-Myers Squibb GmbH Germany.

Study 2013-06-TAB-1: 3020/13

Methods

This was a randomised, open-label, two-period, two-sequence, two-treatment, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Aripiprazole 5 mg tablets (Hexal AG) and Abilify 5 mg tablets (MAH: Bristol Myers Squibb GmbH) in 30 healthy, adult, male human subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Aripiprazole 5 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods each volunteer received a single oral dose of Aripiprazole 5mg tablet with 240ml of water in period I and either one tablet of the reference or test product in period II.

Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 8 hours following drug administration. Drinking water was not permitted one hour before dosing and until one hour post dose. Subjects were confined to BPSI clinical facility from at least 12 hours prior to each drug administration until after the 72-hour blood sample collection in each study period.

The two periods were separated by a wash-out phase of at least 45 days.

Blood samples were taken at the following time points: pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours after dosing. Blood sampling time adjustments are presented in the dossier.

All plasma samples were shipped by courier, frozen in dry ice, and were received frozen and in good condition.

Test and reference products

Product Characteristics	Test product	Reference Product
Name	Aripiprazole 5 mg tablets	Abilify® (Aripiprazole) 5 mg tablets
Strength	5 mg	5 mg
Dosage form	Tablet	Tablet
Manufacturer	[redacted]	Marketing authorization holder: Bristol-Myers Squibb GmbH & Co. KGaA, Germany
Batch number	[redacted]	3D74830
Batch size(Biobatch)	[redacted]	
Measured content(s)[1] (% of label claim)	[redacted]	
Commercial Batch Size	[redacted]	
Expiry date (Retest date)	[redacted]	05/2014
Location of Certificate of Analysis	[redacted]	[redacted]
Member State where the reference product is purchased from:	[redacted]	Germany
This product was used in the following trials:	Study no. 2013-06-TAB-1 [redacted]	Study no. 2013-06-TAB-1 [redacted]

Population(s) studied

30 healthy adult male human subjects were enrolled as per the protocol. The study started with 30 subjects and 27 completed the study. The reasons for 3 exclusions have been included in the dossier and are deemed not to have an effect on the outcome of the study.

Main inclusion criteria:

Healthy human adult literate male non-smoker subjects between 18-45 years of age (inclusive), having a body mass index (BMI) between 18.5 and 30 kg/m2 (inclusive) who had no evidence of underlying disease or clinically significant abnormal laboratory values at screening and who voluntarily consented to participate in the study in written form.

Analytical methods

Analysis of aripiprazole was performed using test method AL-M166-04. This was the same method as used for the 10mg study.

This method involved the extraction of aripiprazole and the internal standard aripiprazole-d8 from human plasma. Samples were kept frozen at -20ºC prior to analysis for a period of 59days.

2718 blood samples were to be collected for the 30 subjects. 1359 samples were collected. No samples were re-assayed and 120 samples were identified for incurred sample reanalysis. 100.00% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

The method has been validated (MVR-166/02) and partially revalidated 8 times. The following parameters were addressed; selectivity of Aripiprazole and the internal standard (IS), calibration curve (linearity), carryover test, recovery of both the analyte and the internal standard, precision, accuracy, dilution integrity accuracy and precision, stability of the stock solution (short and long term stability in the biological matrix, bench top, freeze-thaw, auto sampler storage, and post-preparative stability), haemolysis effect accuracy and precision, ruggedness and matrix effect. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

The effect of interfering drugs was also studied using the following commonly used medicines: caffeine, cetirizine, diclofenac, ibuprofen, paracetamol, nicotine, and ondansetron. No effect on the determination of the analyte and the internal standard was observed.

The lower limit of quantification (LLOQ) of this method for the estimation of Aripiprazole concentrations in plasma was 0.404ng/ml (Precision 3.82%, Accuracy 98.02%). The linearity range of Aripiprazole was from 0.404g/ml to 255.413ng/ml. (8 point curve)

The bioanalytical report (3020/13) was submitted with 20% of the subject chromatograms presented as well as the method SOP. Certificates of analysis for the test and reference drug products as well as for the drug standards used for Aripiprazole and Aripiprazole –d8 have been provided and are deemed acceptable.

Pharmacokinetic Variables

Primary parameters: AUC_{0-72} and C_{max}

Secondary parameters: T_{max}, $t_{½}$, K_{el} and NKEL (Number of points used in the calculation of terminal elimination rate constant).

Bioequivalence criteria: The 90% confidence interval of the relative mean AUC0-72 and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The 90% confidence interval of the relative mean AUC_{0-72} and C_{max} of the test and reference product should be at least 80% and not more than 125% for log-transformed data. ANOVA was performed on the log-transformed pharmacokinetic parameters - AUC_{0-72} and C_{max} of aripiprazole using General Linear Model (PROC GLM procedure) of SAS. The 90% confidence interval for the difference between the least square means (LSM) was calculated for the log-transformed pharmacokinetic parameters - AUC_{0-72} and C_{max} of aripiprazole. The number of observations, arithmetic mean, standard deviation, coefficient of variation (CV %), minimum, median, maximum and geometric mean were calculated for all the pharmacokinetic parameters.

Results

Pharmacokinetic parameters for Aripiprazole 5mg (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$	1005.11	235.551	1070.26	177.779
C_{max}	27.08	6.540	28.03	4.808
T_{max}*	3.04	1.00	3.87	1.758

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

C_{max} maximum plasma concentration

T_{max} time for maximum concentration (* median, range)

Statistical analysis for Aripiprazole 5mg (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$	93.71%	89.33-98.30%	10.26
C_{max}	95.86%	90.03-102.29%	13.71

* estimated from the Residual Mean Squares

Safety data

There were 09 adverse events reported in the study of which all 09 were considered related to the investigational products. AEs that were reported during the study included Vomiting, Upper respiratory tract infection, Backache, Dizziness, Increased SGPT levels, Gastroenteritis and Epigastric Discomfort. Of the related adverse events, 04 were related to test product and 05 were related to reference product. All adverse events were mild to moderate in intensity and resolved completely without sequelae. There were no serious

adverse events reported in this study. Based on the review of the clinical and laboratory safety data, both the study products were found to be safe and well tolerated.

Conclusions

Based on the presented bioequivalence study Aripiprazole 5mg tablets of Hexal AG is considered bioequivalent with Abilify 5mg tablets of Bristol-Myers Squibb GmbH Germany.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Conclusions on clinical aspects

The 5mg, 10mg, 15mg and 30mg strength are generic to the reference product and one new strength is being introduced via the hybrid legal basis (20mg). The proposed 2mg strength was withdrawn during the procedure.

The applicant has conducted two bioequivalence studies in order to support this MAA.

The CHMP considers that based on the presented bioequivalence studies Aripiprazole 5mg tablets of Hexal AG is considered bioequivalent with Abilify 5mg tablets of Bristol-Myers Squibb GmbH Germany and Aripiprazole 10mg tablets of Hexal AG is considered bioequivalent with Abilify 10mg tablets of Bristol-Myers Squibb GmbH Germany. The results with the 10mg tablet formulation can be extrapolated to Aripiprazole 15mg, 20mg and 30mg tablets.

2.5. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC. The CHMP endorsed the Risk Management Plan version 1.4 with the following content:

Safety concerns

Important identified risks	Extrapyramidal symptoms (EPS) including tardive dyskinesia
	Neuroleptic Malignant Syndrome (NMS)
Important potential risks	Seizures
	Hyperglycaemia and diabetes mellitus
	Suicide-related events
	Orthostatic hypotension
	Dyslipidaemia
	Weight gain
	Somnolence / fatigue
Missing information	Safety in pregnancy and lactation
	Safety in paediatrics

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
EPS including tardive dyskinesia	Guidance is given in sections 4.4 “Special warnings and precautions for use” 4.6 “Pregnancy and lactation”, 4.8 “Undesirable effects”, 4.9 “Overdose” and 5.1 “Pharmacodynamic properties” of the SmPC.	Educational material
NMS	Guidance is given in sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the SmPC.	None
Seizures	Guidance is given in sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the SmPC.	None
Hyperglycaemia and diabetes mellitus	Guidance is given in sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the SmPC.	None
Suicide-related events	Guidance is given in sections	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the SmPC.	
Orthostatic hypotension	Guidance is given in sections 4.4 “Special warnings and precautions for use” and 4.8 “Undesirable effects” of the SmPC.	None
Dyslipidaemia	Guidance is given in sections 4.8 “Undesirable effects” and 5.1 “Pharmacodynamic properties” of the SmPC.	None
Weight gain	Guidance is given in sections 4.2 “Posology and method of administration”, 4.4 “Special warnings and precautions for use” 4.8 “Undesirable effects” and 5.1 “Pharmacodynamic properties” of the SmPC.	Educational material
Somnolence / fatigue	Guidance is given in sections 4.2 “Posology and method of administration”, 4.7 “Effects on ability to drive and use machines”, 4.8 “Undesirable effects”, 4.9 “Overdose” and 5.1 “Pharmacodynamic properties” of the SmPC.	Educational material
Safety in pregnancy and lactation	Guidance is given in section 4.6 “Pregnancy and lactation” and 5.3 “Preclinical safety data” of the SmPC.	None
Safety in paediatrics	Guidance is given in sections 4.2 “Posology and method of administration”, 4.4 “Special warnings and precautions for use”, 4.7 “Effects on ability to drive and use machines”, 4.8 “Undesirable effects”, 5.1 “Pharmacodynamic properties” and 5.2 ““Pharmacokinetic properties” of the SmPC.	Educational material

2.7. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the user tested package leaflet of Abilify. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Aripiprazole tablets (5mg, 10mg, 15mg, 30mg strength) and a hybrid of the reference product (20mg strength). The reference product Abilify is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older, treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment as well as treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient. The SmPC is in line with the SmPC of the reference product.

The two bioequivalence studies formed the pivotal basis of the application. The study designs were considered adequate to evaluate the bioequivalence of the two formulations applied for and were in line with the respective European requirements

The test formulations of Aripiprazole Sandoz 5mg tablets and Aripiprazole Sandoz 10 mg tablets met the protocol-defined criteria for bioequivalence when compared with Abilify 5mg and Abilify 10 mg tablets respectively. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Aripiprazole Sandoz in the *treatment of schizophrenia in adults and in adolescents aged 15 years and older, treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment as well as treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older* is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

In each Member State where Aripiprazole Sandoz for the treatment up to 12 weeks of moderate to severe manic episode in Bipolar I Disorder in adolescents aged 13 years and older is launched the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in

each Member State where Aripiprazole Sandoz for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched all healthcare professionals who are expected to prescribe Aripiprazole Sandoz are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet
- Educational material for the healthcare professionals
- Educational material for the patients and their caregivers

Key elements of the Healthcare Professional FAQ Brochure (Q&A format) intended for Healthcare Providers treating adolescent patients with bipolar mania:

- Brief introduction to aripiprazole indication and the purpose of the tool
- Instructions reinforcing that the indicated age range is 13-17 years and that aripiprazole is *not* recommended for use in patients below 13 years of age due to safety concerns
- Instructions that the recommended dose is 10 mg/day and that enhanced efficacy at higher doses has not been demonstrated
- Information regarding the safety and tolerability profile of aripiprazole, in particular potential consequences regarding adverse effects at doses higher than 10 mg/day, in particular with respect to:
    - Weight gain, including a recommendation to monitor patients
    - Extrapyramidal symptoms
    - Somnolence
    - Fatigue
- Reminder to educate patients/caregivers and distribute the Patient/Caregiver Information Brochure

Key elements of the Patients/Caregiver Information Brochure:

- Brief introduction of aripiprazole indication and the purpose of the tool
- Information that the indicated age range is 13-17 years and that aripiprazole is *not* recommended for use in patients below 13 years of age
- Information that aripiprazole can cause adverse effects at doses higher than 10 mg/day, in particular with respect to:
    - Weight gain, including a recommendation to monitor patients
    - Extrapyramidal symptoms
    - Somnolence
    - Fatigue
- Request to inform the physician of all medical conditions before treatment
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.